UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/335,400	11/03/94	PAGE	

EXAMINER	
ADAMS, D	
ART UNIT	**PAPER NUMBER**
1806	4

18M2/0106

E ANTHONY FIGG
ROTHWELL FIGG ERNST & KURZ
555 13TH STREET NW
WASHINGTON DC 20004

DATE MAILED: 01/06/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☒ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-27-34 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 2-26 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-27-34 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☒ been filed in parent application, serial no. 08/155,067 ; filed on 11/23/93.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Applicant is encouraged to note that the preliminary amendment adds eight claims numbered 38-45. The numbering of these claims has been changed according to 37 C.F.R. § 1.126 to 27-34 respectively. Claims 2-26 have been cancelled.

16. A phone call was made to Ms. Ernst on December 22, 1994 regarding a restriction requirement. However, upon further review the restriction requirement has been withdrawn.

17. Claims 1 and 27-34 are currently pending.

18. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: a method for treating a mammal suffering from a T-cell mediated disorder with a CHO glycosylated antibody.

19. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

20. Applicant is invited to notice that box 7 was checked by the draftsman. Applicant is encouraged to amend the specification so that the description of renumbered figure 1 corresponds to the renumbered figures.

21. Applicant is required to submit a proposed drawing correction in response to this Office action. However, correction of the noted defect can be deferred until the application is allowed by the examiner.

22. Applicant has filed affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application, U.S. Serial No. 08/155,864. These affidavits and declarations do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application.

23. Acknowledgment is made of applicant's claim for priority to the 9022543.4 British priority document, under 35 U.S.C. § 119. The certified copy has been filed in parent application, Serial No. 07/777,730, filed on October 16, 1991.

24. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

25. Claim 1 is rejected under 35 U.S.C. § 101 as claiming the same invention as that of claim 1 of copending application Serial No. 08/335,401. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

26. Claims 27-34 are rejected under 35 U.S.C. § 101 because the invention as disclosed is inoperative and therefore lacks utility. There is no evidence presented which clearly and reproducible illustrates that there is any utility for the claimed invention. There is no suggestion that any of the disclosed utilities are attainable or even practical. For example concerning the therapeutic or diagnostic utilities, Waldmann [Science 252:1657-1662 (1991)] teaches that effective therapy using monoclonal antibodies has been elusive and describes limitations of murine antibodies in the therapy of human diseases due to the pharmacokinetic properties of rodent antibodies in human and human anti-mouse antibody responses. Waldmann also indicates that hopes for antibody-based treatment methods engendered by <u>in-vitro</u> and animal model studies have not correlated well with <u>in-vivo</u> clinical trail results in patients. Further Harris et al. [TIBTECH 11:42-44 (1993)] state "there is widespread acceptance that there is little future for the use of rodent mAbs for <u>in vivo</u> human therapy", see page 42, column 2, lines 3-7. Harris et al. also teach "the residual HAMA response to chimeric antibodies is mainly anti-idiotypic, therefore repeated dosing is ineffective", see page 42, column 3, lines 17-20. It is well known in the art that antibody-based therapies have very limited success. One of ordinary skill in the art would not readily accept that Applicant's claimed modified antibodies would be satisfactory for human therapy as asserted in the specification. As evidenced by Osband et al. [Immunotherapy 11(6):193-195 (1990)] one of ordinary skill in the art would not readily accept the utility of an immunotherapeutic agent without convincing objective evidence of efficacy in humans (see paragraph bridging pages 193-194). As further evidenced by Waldmann and Dillman [Ann. Internal Med. 111:592-600 (1989)] it is well known in the art that the use of monoclonal antibodies has, in general, only met with very limited success in humans. Waldmann teaches that immunotoxins have not lived up to expectations and that "the results of <u>in vivo</u> clinical trials in patients with cancer with first-generation immunotoxins did not fulfill the hopes engendered by <u>in vitro</u> and animal model studies" (see page 1660, second column, fourth full paragraph).

Dillman teaches that "as a therapeutic modality, monoclonal antibodies are still promising but their general use will be delayed for several years" (see Abstract). In addition, Hird et al. [Genes and Cancer (1990) chapter 17] teaches that "the data obtained from mouse studies are useful, but cannot be directly translated to apply to the human situation" (see page 185, first full paragraph). Other factors such as proteolytic degradation, immunological inactivation, antigenic modulation or antigen shedding by the tumor, as well as factors influencing localization of the antibody such as the anatomical location of the tumor and its vascularity and blood flow, all have bearing on the efficacy of the antibody therapy. Further, with respect to immunotoxins, the level of antigen expression and the rate and route of internalization also effect the therapeutic efficacy of the antibody. Given the teachings of Osband et al., Waldmann, Dillman, Hird et al. and Harris et al. as well as the other well known factors effecting antibody therapies, one of ordinary skill in the art would not readily accept Applicant's claimed utility on its face, absent some showing of convincing objective evidence of therapeutic or diagnostic utility. Applicant is encouraged to consider Curti [Critical Reviews in Oncology/Hematology 14:29-39 (1993)]. Curti states that "[t]his hostile microenvironment is not duplicated or predicted by any in vitro system and is only partially accounted for by extant computer models. Similarly, animal models employing very small tumor nodules that possess a nascent or absent vascular network do not mimic the physiology discussed here. If the aggregate physiologic behavior of tumor nodules is not taken in to account, then any therapy, no matter how rationally designed or effective in vitro, is likely to be diminished in patients with large tumor burdens [conclusion page 36, column 1, second paragraph]." Therefore, the claims are rejected as lacking patentable utility.

27. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

28. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and for failing to adequately teach how to make and/or use the invention, i.e. for failing to provide an enabling disclosure.

A) Applicants have not disclosed to one of any skill in the art how to use the antibody as a pharmaceutical or therapeutic. There is an insufficient written description of the invention with respect to the in-vivo operability of the antibody to enable one of any skill in the art to use applicant's invention, for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101. Due to the unpredictable nature of the method it would require undue experimentation to obtain applicant's claimed invention from what the specification has disclosed.

29. Claims 27-34 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

30. Claims 27-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 27-34 would read better if an "a" was placed after "treating" on the first line of claim 27.

31. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

32. Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Cabilly et al. [U.S. Patent No. 4,816,567].

33. Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Bodmer et al. [WO 89/01783].

34. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

35. Claims 27-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 38 of copending application Serial No. 08/155,864. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application is drawn to the use of a CHO-glycosylated antibody for treatment of a mammal suffering from a T-cell mediated disorder while the 08/155,864 application is drawn to the use of a CHO-glycosylated antibody for treatment of any disease. The only difference between the two methods is the scope of the method. The 08/155,864 application is broadly drawn to treatment of any disease including a T-cell mediated disorder is therefore considered to be prima facia obvious to a person of ordinary skill in the art at the time the invention was made in view of the invention claimed in the 08/155,864 application. This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

36. The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

37. Claim 27-34 are rejected under 35 U.S.C. § 103 as being unpatentable over Cabilly et al. [U.S. Patent 4,816,567] or Bodmer et al. [WO 89/01783] in view of Benjamin et al. [Nature 320:449-451 (1986)] or Riechmann et al. [Nature 332:323-327 (1988)]. Briefly the claims are drawn, in Jepson format, to a method for treating a mammal suffering from a T cell mediated disorder by administering a therapeutically effective amount of a CHO glycosylated form of the antibody. Cabilly et al. teach altered antibodies [see entire document and abstract] which are expressed in CHO cell lines, column 10, first full paragraph.

Applicant's arguments concerning Cabilly et al. have been considered but were not found persuasive. Cabilly et al. teach altered antibodies that can be expressed in CHO cell lines. Bodmer et al. teach altered antibodies, see entire document. Bodmer et al. teach the use of CHO cells to produce chimeric B72.3 antibody, see pages 21-23. Bodmer et al. teach that this chimeric B72.3 antibody is superior to the murine derivative, see pages 23-24. Bodmer et al. teach that antibodies can be used for the treatment of cancer see page 3 last full paragraph. The antibodies produced by either Cabilly et al. or Bodmer et al. are therefore CHO-glycosylated. Neither Cabilly et al. or Bodmer et al. teach a method for treating a T-cell mediated disorder that is an autoimmune disease, such as MS, GvH, etc. However, Benjamin et al. teach the induction of tolerance by monoclonal antibody therapy using an anti-CD4 antibody, see entire document. This induction of tolerance would obviously treat a T-cell mediated disorder that is an autoimmune disease. Riechmann et al. teach the reshaping of an antibody which recognizes the CDw52, (CAMPATH), antigen for therapeutic use, see entire document. A person of ordinary skill in the art would have been motivated to produce the antibodies of either Benjamin et al. or Riechmann et al. in CHO cells due to the ease of manipulating the cell line and the efficiency of producing the antibody in such a cell line. Therefore it would have been prima facia obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of either Bodmer et al. or Cabilly et al. to those of either Benjamin et al. or Riechmann et al. to obtain a CHO glycosylated antibody useful in a method for treating a mammal suffering from a T cell mediated disorder, including autoimmune disease, such as MS, GvH, etc. The combination of references teach both chimeric and CDR-grafted antibodies.

38. No claims allowed.

39. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4227.

40. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donald E. Adams whose telephone number is (703) 308-0570. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. David Lacey can be reached on (703) 308-3535. The fax phone number for Group 180 is (703) 305-

3014 or (703) 308-4227. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

January 3, 1995

Donald E. Adams, Ph.D.
Patent Examiner
Group 1800